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Original Article

Impact of initial fluid resuscitation volume on clinical outcomes in patients with heart failure and septic shock

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ABSTRACT

Background: Fluid resuscitation is a key treatment for sepsis, but limited data exists in patients with existing heart failure (HF) and septic shock. The objective of this study was to determine the impact of initial fluid resuscitation volume on outcomes in HF patients with reduced or mildly reduced left ventricular ejection fraction (LVEF) with septic shock.

Methods: This multicenter, retrospective, cohort study included patients with known HF (LVEF ≤50%) presenting with septic shock. Patients were divided into two groups based on the volume of fluid resuscitation in the first 6 h; <30 mL/kg or ≥30 mL/kg. The primary outcome was a composite of in-hospital mortality or renal replacement therapy (RRT) within 7 days. Secondary outcomes included acute kidney injury (AKI), initiation of mechanical ventilation, and length of stay (LOS). All related data were collected and compared between the two groups. A generalized logistic mixed model was used to assess the association between fluid groups and the primary outcome while adjusting for baseline LVEF, Acute Physiology and Chronic Health Evaluation (APACHE) II score, inappropriate empiric antibiotics, and receipt of corticosteroids.

Results: One hundred and fifty-four patients were included (93 patients in <30 mL/kg group and 61 patients in ≥30 mL/kg group). The median weight-based volume in the first 6 h was 17.7 (12.2–23.0) mL/kg in the <30 mL/kg group *vs.* 40.5 (34.2–53.1) mL/kg in the ≥30 mL/kg group (P <0.01). No statistical difference was detected in the composite of in-hospital mortality or RRT between the <30 mL/kg group compared to the ≥30 mL/kg group (55.9% *vs.* 45.9%, P=0.25), respectively. The <30 mL/kg group had a higher incidence of AKI, mechanical ventilation, and longer hospital LOS.

Conclusions: In patients with known reduced or mildly reduced LVEF presenting with septic shock, no difference was detected for in-hospital mortality or RRT in patients who received ≥30 mL/kg of resuscitation fluid compared to less fluid, although this study was underpowered to detect a difference. Importantly, ≥30 mL/kg fluid did not result in a higher need for mechanical ventilation.

Introduction

Sepsis accounts for nearly 10% of all hospitalizations in the United States (US) and represents a significant financial burden to healthcare systems.[1,2] Outcomes for this condition have improved over the past two decades, but septic shock-related mortality remains greater than 40%.[3,4] Current guidelines emphasize the importance of early recognition of sepsis, intravenous (IV) fluid resuscitation, and timely initiation of antimicrobials. Specific guidance provided by the Surviving Sepsis Campaign (SSC) recommends administration of at least 30 mL/kg of crystalloid within the first 3 h of re-

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suscitation, regardless of existing comorbidities. However, it should be noted that the SSC guidelines recommendation for fluid volume is a weak recommendation based on low-quality evidence.[5]

It is estimated that nearly 50% of hypotensive patients may be fluid non-responders according to dynamic assessments of fluid responsiveness (i.e., stroke volume variation, passive leg raise, fluid challenge), regardless of cardiac function.[6–8] Additional volume in these patients may lead to volume overload, pulmonary edema, acute lung injury, and other organ dysfunction.[9–12] Patients with pre-existing cardiac dysfunction may be particularly vulnerable to over-resuscitation and more susceptible to the adverse consequences of a net positive fluid balance.[11–15] As such, it is prudent to be cognizant that these patients often have a lower fluid tolerance, or ability to accommodate fluids prior to developing organ dysfunction, and may require frequent modifications to resuscitation based on clinical signals including physical exam, radiographic examination, and point of care ultrasound, to ensure adequate end-organ perfusion without causing congestion.[16] It is unknown if the SSC resuscitation recommendation should be applied to sepsis patients with known heart failure (HF) as limited data exist regarding the impact of initial fluid resuscitation volume on this population. The purpose of this study was to compare morbidity and mortality between patients with known HF with a reduced or mildly reduced left ventricular ejection fraction (LVEF) and septic shock who received <30 mL/kg *vs.* ≥30 mL/kg of initial fluid resuscitation volume.

Methods

Study design

A multicenter, retrospective, cohort study was conducted at four US academic medical centers (The Ohio State University Wexner Medical Center, Corewell Health, Nebraska Medicine, and Huntsman Cancer Institute at the University of Utah) and compared patients with septic shock and known HF with an LVEF ≤50% who received ≥30 mL/kg *vs.* <30 mL/kg of initial IV fluid resuscitation volume based on actual body weight within the first 6 h of sepsis onset. Adult patients 18–89 years of age with an International Classification of Diseases, Ninth Edition (ICD-9) or Tenth Edition (ICD-10) code for septic shock and HF admitted to the intensive care unit (ICU) between October 2011 and August 2018 were eligible for inclusion. All patients identified were manually reviewed within the electronic medical record to determine if they met the criteria for inclusion based on the following definitions. Septic shock was defined as the presence of two systemic inflammatory response syndrome (SIRS) criteria with confirmed or suspected infection and receipt of vasopressors of maintaining mean arterial pressure (MAP) ≥65 mmHg despite initial fluid resuscitation (at least 500 mL) in the absence of hypovolemia.[17] Sepsis onset was defined as the time of first fluid bolus administration (time zero) after fulfilling sepsis criteria. A 12-h period prior to vasopressor initiation was evaluated to determine sepsis onset for patients who developed sepsis after hospital admission. Patients were assessed for HF using echocardiography within 2 years prior to the index admission and only those with an LVEF ≤50% were included. The report from the most recent image prior to the index admission was assessed for baseline LVEF when multiple echocardiograms were available. Patients meeting any of the following criteria were excluded: end-stage renal disease (ESRD), history of pulmonary arterial hypertension (PAH), receipt of resuscitation fluids prior to transfer from an outside hospital, admission to the ICU from the operating room or following traumatic injury, transition to comfort care within 6 h, evidence of acute myocardial ischemia (MI), pregnant, or incarcerated. Only the initial episode of septic shock was analyzed during each hospital encounter. The study was approved by the institutional review board (IRB) at each participating institution. A waiver of informed consent was obtained from the IRB for this study.

Outcomes

The primary outcome was a composite of in-hospital mortality or the initiation of renal replacement therapy (RRT) within the first 7 days of sepsis onset. Secondary outcomes included time to hemodynamic stability (time zero to cessation of vasopressor/inotropic support and a MAP >65 mmHg for at least 12 h), percentage of patients with lactate <2 mmol/L within 24 h, initiation and duration of mechanical ventilation, fluid balance at the end of hospital days 3 and 7 from time zero, development of acute kidney injury (AKI) within 7 days from time zero, and hospital and ICU length of stay (LOS). AKI was assessed according to the RIFLE (risk, injury, failure, loss of function, and end-stage kidney disease) criteria using only the Risk, Injury, and Failure components.[18] Patients requiring RRT were classified as Failures.

Data collection

Demographic information, past medical history, severity of illness, and laboratory values were collected at baseline. Obesity was defined as a body mass index ≥30 kg/m^2. The volume and type of IV resuscitation fluid were collected from the first fluid bolus to 6 h and from 6 h to 72 h. Fluid balance was documented at the end of hospital days 1, 3, and 7 from time zero. Data regarding the suspected source of infection, microbiologic cultures, and time to appropriate antimicrobial therapy was collected. Empiric antibiotics were considered appropriate in two scenarios: (1) if cultures were positive and the pathogen was susceptible to the empiric antibiotics, and (2) if all cultures were negative and empiric antibiotics were appropriate based on the site and origin of infection. The time to the first antibiotic dose was calculated as the difference between time zero and the first antibiotic dose. Administration of corticosteroids, vasopressors, inotropes, loop diuretics, and nephrotoxins was recorded within 7 days of time zero.

Statistical analysis

Patients were grouped based on the IV fluid volume received in the first 6 h after sepsis onset; <30 mL/kg or ≥30 mL/kg based on actual body weight. Normally distributed, continuous data are presented as means±standard deviation, and non-normally distributed, continuous data are presented as medians (interquartile range). The aforementioned data were analyzed using the Student's *t*-test and Wilcoxon rank-sum test, respectively.

Nominal data were analyzed using Fisher's exact test. A generalized logistic mixed model was used to assess the association between fluid groups and the primary outcome while adjusting for baseline LVEF, Acute Physiology and Chronic Health Evaluation (APACHE) II score, inappropriate empiric antibiotics, and receipt of corticosteroids. A random intercept was included to account for differences across sites. Results are reported as odds ratio and 95% confidence interval. Time to hemodynamic stability was assessed using cumulative incidence curves which were compared between fluid groups using the log-rank test. For these curves, time was measured as hours from the initiation of vasopressors until hemodynamic stability; patients who died without reaching stability were censored at their time of death. We estimated that 218 patients would be needed to have 80% power to detect a 20% difference in the primary outcome at an alpha level of 0.05 assuming 50% of patients in the ≥30 mL/kg group would have the primary outcome. Study data were collected and managed using REDCap electronic data capture tools hosted at The Ohio State University. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.[19,20] All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). A significant level of 0.05 was used for comparisons.

Results

Overall, 2062 patients were screened for study inclusion. The primary reasons for exclusion were transferred from an outside hospital or ESRD on admission. A total of 154 patients were included in the final analysis (93 patients in the <30 mL/kg group and 61 patients in the ≥30 mL/kg group). Baseline characteristics are presented in (Table 1). Patients were predominantly Caucasian males, had an LVEF ≤40%, and were suspected to have respiratory or bloodstream infections. The <30 mL/kg group had a higher incidence of obese patients. Additionally, patients admitted directly to the ICU or from a hospital floor more commonly received <30 mL/kg initial fluid resuscitation.

Fluid volumes received at various time points from sepsis onset are included in (Table 2). The median volume of fluid received in the first 6 h from time zero between patients in the ≥30 mL/kg group and the <30 mL/kg group was 3000 (2500–4000) mL *vs.* 1500 (1000–2000) mL (P <0.01), respectively. This correlated to a median actual body weight-based volume of fluid of 40.5 (34.2–53.1) mL/kg *vs.* 17.7 (12.2–23.0) mL/kg (P <0.01), respectively. In addition to receiving more fluid in the first 6 h, the ≥30 mL/kg group received more total volume of fluid by the end of hospital day 1 (P=0.01).

The primary outcome of in-hospital mortality or RRT in the first 7 days occurred in 55.9% of patients in the <30 mL/kg group and 45.9% in the ≥30 mL/kg group (P=0.25). All univariate outcomes between groups are displayed in (Table 3). The results of the multivariable analysis are presented in (Table 4). After adjusting for baseline LVEF, APACHE II score, inappropriate empiric antibiotics, and receipt of corticosteroids, the volume of fluid received in the first 6 h of septic shock onset was not significantly associated with the composite of in-hospital mortality or RRT. APACHE II score and receipt of corticosteroids were the only independent variables associated with the primary outcome.

Due to the difference between groups in obesity incidence, a *post hoc* analysis of the primary outcome was performed based on adjusted and ideal body weight (Table 5). The impact of the fluid group on the primary outcome remained insignificant after normalizing the volume of fluid received in the first 6 h for adjusted and ideal body weights.

Overall, 106 patients (68.8%) reached hemodynamic stability with a median time of 54 h *vs.* 44 h for the <30 mL/kg group and the ≥30 mL/kg group, respectively (P=0.41). Although patients in the ≥30 mL/kg group had a larger net positive fluid

Table 1
Baseline characteristics and clinical variables between fluid groups.

Characteristic	<30 mL/kg group (n=93)	≥30 mL/kg group (n=61)	P-value
Age (years)	63.6 ± 14.9	63.6 ± 11.9	0.99
Male	60 (64.5)	32 (52.5)	0.18
Race			0.50
Caucasian	56 (60.2)	42 (68.9)	
Black	17 (18.3)	10 (16.4)	
Other	20 (21.5)	9 (14.8)	
Body mass index (kg/m^2)	29.3 (23.7–36.8)	25.4 (20.0–28.3)	<0.01
Obese	45 (48.4)	11 (18.0)	<0.01
Source of admission			0.05
Emergency department	43 (46.2)	40 (65.6)	
Hospital floor	46 (49.5)	18 (29.5)	
Direct to ICU	4 (4.3)	3 (4.9)	
LVEF			0.15
<30%	33 (35.5)	13 (21.3)	
30–40%	33 (35.5)	24 (39.3)	
>40–50%	27 (29.0)	24 (39.3)	
Charlson comorbidity index	6 (4–8)	7 (5–9)	0.13
APACHE II score	28 (21–34)	27 (20–34)	0.75
SOFA score	10 (7–12)	9 (7–12)	0.60
Baseline lactate (mmol/L)	2.20 (1.30–3.75)	2.67 (1.68–4.65)	0.14
Suspected infection source			
Respiratory	43 (46.2)	23 (37.3)	0.32
Blood/line	37 (39.8)	27 (44.3)	0.62
Urinary	20 (21.5)	13 (21.3)	1.00
Intra-abdominal	14 (15.1)	4 (6.6)	0.13
Skin and soft tissue	7 (7.5)	3 (4.9)	0.74
Other	6 (6.5)	6 (9.8)	0.54
Microbiologic cultures			
Gram-negative	34 (36.6)	27 (44.3)	0.40
Gram-positive	32 (34.4)	26 (42.6)	0.31
No growth	26 (28.0)	15 (24.6)	0.71
Viral	5 (5.4)	2 (3.3)	0.70
Fungal	4 (4.3)	6 (9.8)	0.20
C. difficile	4 (4.3)	2 (3.3)	1.00
Time to first antibiotics (h)	0.0 (−12.0–1.1)	0.5 (−0.6–1.5)	0.16
Empiric antibiotics appropriate	73 (78.5)	50 (82.0)	0.68
Corticosteroids	42 (45.2)	19 (31.2)	0.09
Vasopressors and inotropes			
Norepinephrine	91 (97.9)	60 (98.4)	1.00
Epinephrine	18 (19.4)	8 (13.1)	0.38
Vasopressin	27 (29.0)	18 (29.5)	1.00
Phenylephrine	14 (15.1)	3 (4.9)	0.06
Dopamine	8 (8.6)	1 (1.6)	0.09
Milrinone	3 (3.2)	1 (1.6)	1.00
Dobutamine	8 (8.6)	6 (9.8)	0.78
Loop diuretic	40 (43.0)	22 (36.1)	0.39

Data presented as mean ± standard deviation, median (interquartile range) or n (%).
APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit; LVEF: Left ventricular ejection fraction; SOFA: Sequential organ failure assessment.

Table 2
IV volume of fluid received from time zero to the end of day 3 between fluid groups.

Variable	<30 mL/kg group (*n*=93)	≥30 mL/kg group (*n*=61)	*P*-value
IV fluid volume from 0 h to 6 h (mL)			
Total	1500 (1000–2000)	3000 (2500–4000)	<0.01
0.9% sodium chloride	1000 (1000–2000)	3000 (2000–3000)	<0.01
Balanced fluid	1000 (1000–2000)	1000 (1000–2000)	0.49
Albumin	400 (250–1000)	500 (500–500)	NA
Actual weight-based fluid from 0 h to 6 h (mL/kg)	17.7 (12.2–23.0)	40.5 (34.2–53.1)	<0.01
Total fluid intake (mL)			
Day 1	4181 (2784–6520)	5123 (3866–7642)	0.01
Day 2	2952 (1737–4918)	2220 (1580–4739)	0.40
Day 3	1816 (835–3281)	2056 (944–3572)	0.49

Data presented as median (interquartile range).
IV: Intravenous; NA: Not available.

Table 3
Primary and secondary outcomes between fluid groups.

Outcome	<30 mL/kg group (*n*=93)	≥30 mL/kg group (*n*=61)	*P*-value
Primary outcome			
Composite outcome	52 (55.9)	28 (45.9)	0.25
RRT	23 (24.7)	11 (18.0)	0.43
In-hospital mortality	43 (46.2)	24 (39.3)	0.41
Lactate clearance	43 (65.2)	27 (62.8)	0.84
AKI	44 (47.3)	16 (26.7)	<0.01
Risk	17/44 (38.6)	7/16 (43.8)	0.72
Injury	14/44 (31.8)	4/16 (25.0)	0.76
Failure	13/44 (29.5)	5/16 (31.3)	1.00
MV	62 (66.7)	30 (49.2)	0.04
Duration of MV (h)	80 (43–189)	76 (48–192)	0.95
Net fluid balance (mL)			
Day 1	3161 (1626–4937)	3841 (2738–6566)	0.04
Day 3	5629 (2769–9237)	6520 (3438–10,111)	0.34
Day 7	5538 (1810–10,888)	7850 (3129–11,790)	0.16
LOS (days)			
ICU	5 (2–11)	4 (2–7)	0.13
Hospital	12 (6–21)	8 (5–13)	<0.01

Data presented as mean ± standard deviation, median (interquartile range) or *n* (%).
AKI: Acute kidney injury; ICU: Intensive care unit; LOS: Length of stay; MV: Mechanical ventilation; RRT: Renal replacement therapy.

Table 4
Multivariable logistic regression model of the effect of fluid group on the odds of in-hospital mortality or need for RRT.

Variable	Odds ratio (95% CI)	*P*-value
Fluid amount		
<30 mL/kg	1.56 (0.70–3.47)	0.27
≥30 mL/kg	Ref.	
LVEF		
<30%	Ref.	0.32
30–40%	1.87 (0.72–4.87)	
>40–50%	1.04 (0.39–2.79)	
APACHE II score	1.12 (1.07–1.18)	<0.01
Inappropriate empiric antibiotics	1.10 (0.42–2.88)	0.86
Corticosteroids	3.91 (1.74–8.78)	0.01

APACHE: Acute physiology and chronic health evaluation; CI: Confidence interval; LVEF: Left ventricular ejection fraction; Ref.: Reference; RRT: Renal replacement therapy.

balance at the end of day 1, there was no statistically significant difference between groups in total fluid intake or balance at the end of hospital day 2 or 3. More patients in the <30 mL/kg group required mechanical ventilation, developed AKI, and had a longer hospital LOS (Table 3). No difference in the duration of mechanical ventilation was detected between groups.

Table 5
Assessment of the primary outcome between fluid groups based on different body weights.

Variable	<30 mL/kg group	≥30 mL/kg group	*P*-value
Actual weight-based fluid			
n	93	61	
Composite outcome	52 (55.9)	28 (45.9)	0.25
RRT	23 (24.7)	11 (18.0)	0.43
Mortality	43 (46.2)	24 (39.3)	0.41
Ideal weight-based fluid			
n	67	87	
Composite outcome	35 (52.2)	45 (51.7)	1.00
RRT	15 (22.4)	19 (21.8)	1.00
Mortality	30 (44.8)	37 (42.5)	0.87
Adjusted weight-based fluid			
n	81	73	
Composite outcome	43 (53.1)	37 (50.7)	0.87
RRT	17 (21.0)	17 (23.3)	0.85
Mortality	37 (45.7)	30 (41.1)	0.63

Data presented as *n* (%).
RRT: Renal replacement therapy.

Discussion

Fluid overload in patients with sepsis has been associated with worsening organ dysfunction and mortality and the negative consequences of fluid overload may be more detrimental in patients with a past medical history of HF.[9–12] Therefore, the current study sought to compare the impact of <30 mL/kg *vs.* ≥30 mL/kg of initial resuscitation volume on outcomes in patients presenting with septic shock with known LVEF ≤50% prior to admission. The volume of IV fluid resuscitation during the first 6 h of sepsis onset was not associated with a difference in the composite outcome of in-hospital mortality or RRT, however, this study was underpowered to detect a difference in this outcome. The lack of association persisted after multivariable logistic regression and a *post hoc* analysis that normalized initial resuscitation volume for ideal and adjusted body weights. Importantly, our study excluded additional comorbidities that may influence initial fluid resuscitation, such as ESRD, PAH, and acute MI. Despite no statistical difference between fluid groups for the primary outcome, patients in the <30 mL/kg group did have a longer hospital LOS (12 days *vs.* 8 days, *P* <0.01), higher rates of AKI (47.3% *vs.* 26.7%, *P* <0.01), and a higher need for mechanical ventilation (66.7% *vs.* 49.2%, *P*=0.04). However, lactate clearance and duration of mechanical ventilation were similar between groups. There are several factors that may have

contributed to this trend toward worse outcomes in patients receiving <30 mL/kg initial volume fluid resuscitation. Baseline characteristics reflect that a greater percentage of patients in the <30 mL/kg group had an LVEF <30% (35.5% *vs.* 21.3%) reflecting higher severity of illness and that this group may have been at higher risk for volume overload. It is not surprising that patients with a lower LVEF at baseline were more likely to receive <30 mL/kg initial volume of resuscitative fluids, as clinicians may be more cautious with fluid resuscitation in patients with severe cardiac dysfunction. Patients with a lower LVEF may not be able to tolerate additional fluid administration and dynamic assessments of fluid responsiveness were unable to be determined due to the retrospective nature of this study. Additionally, there may be limitations to including RRT within 7 days of initial resuscitation as part of the compositive primary outcome. This outcome was selected with an attempt at capturing both the safety and efficacy of resuscitation volume as the initiation of RRT was thought to be a surrogate for volume overload in the setting of acute renal failure in the context of HF. Outcomes such as duration of shock, rates of AKI, and need for mechanical ventilation may be more clinically relevant in this patient population.

One possible explanation for the lack of difference detected in our primary outcome could be the similar net fluid balances between groups after the initial resuscitation phase. The two comparison groups in this study had no difference in the net fluid balance at the end of hospital day 3 or 7, despite the >30 mL/kg group receiving more resuscitation fluid in the first 6 h and total fluid by the end of day 1. This is consistent with a previous study that suggested a higher late fluid balance (>24 h) was associated with worse outcomes, including increased mortality.[21] It is alternatively possible that if patients in the <30 mL/kg group had more severe LV impairment, their pulmonary circuit may have been more easily overloaded, despite the lesser initial volume.

Multivariable logistic regression identified only two predictive variables of the primary outcome: APACHE II score and the use of corticosteroids. APACHE II is a validated scoring index that can prognostically stratify acutely ill patients and its association with our primary outcome supports the reliability of our model.[22] Corticosteroids' independent association with the primary outcome may suggest they were initiated in patients requiring high-dose of multiple vasopressors who would have been at higher risk for poor outcomes, as previous studies have suggested either improvement or no effect on mortality.[23–26]

Our study results also indicate that patients admitted from the emergency department were more likely to receive >30 mL/kg initial fluid volume for resuscitation than those admitted from the hospital floor (received in 65.6% of those admitted from the emergency department compared to 29.5% admitted from a hospital ward). This could have reflected differences in the severity of illness between groups, variation in practitioner knowledge of guideline recommendations or resuscitation protocols based on setting, or practitioner access to information available pertaining to current volume status at the time of resuscitation. While not able to determine the specific reason for this variation in practice retrospectively, it could have influenced study outcomes. Additionally, the current study utilized a 6-h time frame for initial resuscitation while the SSC, as well as SEP-1 core measures, recommend 30 mL/kg of fluid within 3 h of sepsis onset.[5] The 6-h time frame utilized in the present study has been previously utilized in landmark trials assessing the impact of early goal-directed therapy (EGDT).[27–30]

Our results are consistent with Ouellette and Shah[31] who performed a retrospective case–control analysis of septic patients to determine predictors of mortality in those with pre-existing left ventricular (LV) dysfunction (LVEF ≤50%) compared to those with normal cardiac function. There was no difference in 24-h fluid administered between groups; however, patients with an LVEF <35% received less fluid than patients with an LVEF 35–50% (3.4 L *vs.* 4.4 L, P=0.012). There was no difference in in-hospital mortality between those with and without LV dysfunction (32% *vs.* 23.4%, P=0.117), but risk factors for mortality in those with LV dysfunction included the following: intubation status, low $ScvO_2$, failure to comply with the sepsis bundle, and a source of infection other than the lungs. Unfortunately, the authors did not report the volume of initial resuscitation fluid received in the first 3 h or 6 h from sepsis onset, and <50% of patients required vasopressors making it difficult to discern the impact of initial fluid resuscitation on outcomes in a population presenting with septic shock.

In contrast to the prior study, Abou Dagher et al.[32] evaluated the impact of congestive heart failure (CHF; LVEF ≤40%) on in-hospital mortality in septic patients. Those with CHF had higher in-hospital mortality and despite receiving less fluid in the first 24 h, were more likely to require furosemide, mechanical ventilation, and dobutamine during that same period. Our results revealed no differences between groups in the use of vasopressors, inotropes, or loop diuretics within 7 days, and the severity of cardiac dysfunction based on baseline LVEF did not significantly increase the incidence of poor outcome after multivariable logistic regression (Tables 1 and 3).

Contrary to expectation, the incidence of mechanical ventilation was higher in patients who received <30 mL/kg *vs.* ≥30 mL/kg, 66.7% *vs.* 49.2% (P=0.043), respectively. It is possible that patients in the <30 mL/kg group displayed signs of more severe cardiac dysfunction that resulted in less resuscitation fluid being administered; however, given the retrospective design of this study, we are unable to determine the rationale for the volume of fluid administered. Alternatively, while our groups were relatively similar at baseline and respiratory sources of infection were not statistically different, the higher rate of obesity in the <30 mL/kg group may have impacted the higher rate of mechanical ventilation. Compared to normal-weight septic patients, obese patients may have a greater incidence and duration of mechanical ventilation.[33] At least one report has, however, concluded that patients at high risk of over-resuscitation may not have worse respiratory outcomes with aggressive initial fluid resuscitation. Khan et al.[34] assessed the impact of restricted (<30 mL/kg) *vs.* standard (≥30 mL/kg) resuscitation strategies on the need for mechanical ventilation within 72 h of initial resuscitation in patients with cirrhosis, ESRD, or HF presenting with sepsis or septic shock. Administration of ≥30 mL/kg of fluid did not increase intubation rates, time to intubation, or the duration of mechanical ventilation, but outcomes were not delineated by comorbidity and only 22% of patients had an LVEF ≤40%.[34] The volume of fluid received in the first 6 h in the <30 mL/kg group *vs.* ≥30 mL/kg group was similar to our study (16 mL/kg *vs.* 18 mL/kg and 41 mL/kg *vs.* 41 mL/kg, respectively), but we included only patients with septic shock, had more patients with a baseline LVEF ≤40% (67%

vs. 22%), and specifically excluded those with ESRD to avoid the confounding effect this may have on initial fluid resuscitation.

Limitations

This study had several limitations. Despite the multicenter design, the sample was unable to meet adequate power to detect a difference in the primary outcome and detection of a 20% difference in this outcome based on fluid volume may not be realistic. Our retrospective design relied on the accuracy of documented information and could be confounded by unmeasured information. Most importantly, we were unable to collect dynamic assessment of fluid challenges and fluid responsiveness that would guide the decision to administer additional volumes of resuscitative fluid. Furthermore, it was not possible to control for additional factors that may have influenced the volume of resuscitation fluid patients received in the first 6 h, including baseline LVEF. It is possible clinicians may have restricted additional fluid in patients in the <30 mL/kg group if overt signs of cardiac dysfunction and volume overload were present making a correlation between fluid received and outcomes difficult to ascertain. Nearly one-fourth of patients had presumed culture-negative septic shock and may have had an alternative shock etiology. Differentiation of septic shock from other shock states including cardiogenic is difficult in the absence of invasive hemodynamic monitoring, especially in patients with pre-existing cardiac dysfunction. It is therefore plausible that a portion of patients in this study had other etiologies of shock, although the low number of patients who received inotropes, including milrinone and dobutamine, may indicate that cardiogenic shock was not felt to be the primary etiology by the treating clinician. An attempt to mitigate this possibility was made by utilizing SIRS criteria and requiring vasopressors in the setting of suspected or known infection, which is based on established criteria and the incidence of culture-negative septic shock in this study was similar to a previous report.[35] It is possible the LVEF threshold of ≤50% may have recruited patients without systolic failure, and since diastolic dysfunction and valvular disorders were not collected, we cannot exclude the possibility that some patients may not have met classic criteria for HF or determine the impact these had on outcomes. It should be noted, however, most patients (67%) had a baseline LVEF ≤40% within 2 years prior to the index admission, suggesting most patients had at least systolic dysfunction, although the authors acknowledge there is likely substantial variability to fluid response even amongst patients with an LVEF ranging from 5% to 40%.

Conclusions

This study found no significant difference in the composite incidence of in-hospital mortality or RRT based on IV resuscitation volume received in the first 6 h after sepsis onset for patients presenting with septic shock and known HF with a baseline LVEF ≤50%. Secondary outcomes were worse outcomes in patients receiving <30 mL/kg initial fluid including longer hospital LOS, higher rates of AKI, and a higher need for mechanical ventilation although patients in this group may have been at higher risk at baseline as this group included a larger percentage of patients with left ventricle end-diastolic dimension (LVED) <30%. Since the sample size included did not meet statistical power to detect a difference in the primary outcome, additional studies are needed to assist in guiding initial fluid resuscitation in this patient population.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. JAMA 2017;318(13):1241–9. doi:10.1001/jama.2017.13836.
[2] Torio CM, Moore BJ. National Inpatient Hospital Costs: the most expensive conditions by payer, 2013. In: Healthcare cost and utilization project (HCUP) statistical briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006. doi:10.1377/hlthaff.2015.1194.3.
[3] Kadri SS, Rhee C, Strich JR, Morales MK, Hohmann S, Menchaca J, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. Chest 2017;151(2):278–85. doi:10.1016/j.chest.2016.07.010.
[4] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–10. doi:10.1001/jama.2016.0287.
[5] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021;49(11):e1063–143. doi:10.1097/CCM.0000000000005337.
[6] Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002;121(6):2000–8. doi:10.1378/chest.121.6.2000.
[7] Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? JAMA 2016;316(12):1298–309. doi:10.1001/jama.2016.12310.
[8] Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. Chest 2013;143(2):364–70. doi:10.1378/chest.12-1274.
[9] Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care 2011;1(1):1. doi:10.1186/2110-5820-1-1.
[10] Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136(1):102–9. doi:10.1378/chest.08-2706.
[11] Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. Crit Care 2013;17(5):R246. doi:10.1186/cc13072.
[12] Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock 2015;43(1):68–73. doi:10.1097/SHK.0000000000000268.
[13] Ognibene FP, Parker MM, Natanson C, Shelhamer JH, Parrillo JE. Depressed left ventricular performance. Response to volume infusion in patients with sepsis and septic shock. Chest 1988;93(5):903–10. doi:10.1378/chest.93.5.903.
[14] Leisman DE, Doerfler ME, Schneider SM, Masick KD, D'Amore JA, D'Angelo JK. Predictors, prevalence, and outcomes of early crystalloid responsiveness among initially hypotensive patients with sepsis and septic shock. Crit Care Med 2018;46(2):189–98. doi:10.1097/CCM.0000000000002834.
[15] Sirvent JM, Ferri C, Baró A, Murcia C, Lorencio C. Fluid balance in sepsis and septic shock as a determining factor of mortality. Am J Emerg Med 2015;33(2):186–9. doi:10.1016/j.ajem.2014.11.016.
[16] Kattan E, Castro R, Miralles-Aguiar F, Hernández G, Rola P. The emerging concept of fluid tolerance: a position paper. J Crit Care 2022;71:154070. doi:10.1016/j.jcrc.2022.154070.
[17] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644–55. doi:10.1378/chest.101.6.1644.
[18] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky PAcute Dialysis Quality Initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204–12. doi:10.1186/cc2872.

[19] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81. doi:10.1016/j.jbi.2008.08.010.
[20] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. doi:10.1016/j.jbi.2019.103208.
[21] Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. Crit Care Med 2017;45(3):386–94. doi:10.1097/CCM.0000000000002189.
[22] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29. doi:10.1097/00003246-198510000-00009.
[23] Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288(7):862–71. doi:10.1001/jama.288.7.862.
[24] Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378(9):797–808. doi:10.1056/NEJMoa1705835.
[25] Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378(9):809–18. doi:10.1056/NEJMoa1705716.
[26] Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358(2):111–24. doi:10.1056/NEJMoa071366.
[27] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77. doi:10.1056/NEJMoa010307.
[28] Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al., ProCESS Investigators A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370(18):1683–93. doi:10.1056/NEJMoa1401602.
[29] Peake SL, Delaney A, Bailey M, Bellomo R, et al., ARISE Investigators, ANZICS Clinical Trials Group Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371(16):1496–506. doi:10.1056/NEJMoa1404380.
[30] Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372(14):1301–11. doi:10.1056/NEJMoa1500896.
[31] Ouellette DR, Shah SZ. Comparison of outcomes from sepsis between patients with and without pre-existing left ventricular dysfunction: a case-control analysis. Crit Care 2014;18(2):R79. doi:10.1186/cc13840.
[32] Abou Dagher G, Hajjar K, Khoury C, El Hajj N, Kanso M, Makki M, et al. Outcomes of patients with systolic heart failure presenting with sepsis to the emergency department of a tertiary hospital: a retrospective chart review study from Lebanon. BMJ Open 2018;8(7):e022185. doi:10.1136/bmjopen-2018-022185.
[33] Li S, Hu X, Xu J, Huang F, Guo Z, Tong L, et al. Increased body mass index linked to greater short- and long-term survival in sepsis patients: a retrospective analysis of a large clinical database. Int J Infect Dis 2019;87:109–16. doi:10.1016/j.ijid.2019.07.018.
[34] Khan RA, Khan NA, Bauer SR, Li M, Duggal A, Wang X, et al. Association between volume of fluid resuscitation and intubation in high-risk patients with sepsis, heart failure, end-stage renal disease, and cirrhosis. Chest 2020;157(2):286–92. doi:10.1016/j.chest.2019.09.029.
[35] Gupta S, Sakhuja A, Kumar G, McGrath E, Nanchal RS, Kashani KB. Culture-negative severe sepsis: nationwide trends and outcomes. Chest 2016;150(6):1251–9. doi:10.1016/j.chest.2016.08.1460.